INFLUENCE OF THE PACING SITE ON THE VENTRICULAR EFFECTIVE REFRACTORY PERIOD

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The ventricular effective refractory periods (VERP) were evaluated in 7 patients (5 male, mean age 52 years), with either documented or suspected VT. The RV apex VERP was determined at 2 paced cycle lengths (PCL) by the extrastimulus method using a RV, LV and RA drive cycle. The LV apex VERP was determined using the same pacing sites and PCLs. Local electrograms on the extrastimulus electrode were used to eliminate the effects of intracardiac conduction. VERP prolonged significantly as the drive site was removed from the extrastimulus site at both PCLs ($p < 0.03$ for RV and LV).

Results (ms) Drive site	Extrastimulus	PCL 527±66 VERP	PCL 409±28 VERP
RV	RV	221±19	210±16
RA	RV	246±22	219±20
LV	RV	269±20	241±35
LV	LV	228±33	209±21
RV	LV	246±24	229±26
RA	LV	256±19	230±16

A 3D computer model (3375 cells) of myocardial excitation and recovery which reproduced the electrotonic interactions (EI) between myocytes was used to verify hypotheses of the mechanism underlying the observations. The model experiments evaluated the effects of (a) the area captured by a stimulus, (b) the differences between the action potentials of directly paced cells and cells excited by the conducted activation, (c) EI examined separately for the action potential excitation and recovery phases. The model reproduced the measured phenomenon when simulating (A) EI during both excitation and repolarisation, (B) the pacing stimulus activating several tens of cells, and (C) the action potentials of the artificially stimulated cells having a prolonged depolarisation plateau and faster repolarisation. The presence of all phenomena (A-C) was necessary for the reproduction of the observed differences in VERP of the paced and remote areas.

5-FLUOROURACIL INDUCES VASOCONSTRICTION OF VASCULAR SMOOTH MUSCLE IN VITRO: EVIDENCE THAT VASOSPASM IS THE BASIS FOR CARDIOVASCULAR AND CEREBROVASCULAR ISCHEMIC COMPLICATIONS OF 5-FLUOROURACIL

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Clinical reports have indicated that the prevalence of acute cardiovascular and cerebrovascular (CV) ischemic events among pts receiving 5-fluorouracil (5-FU) approaches 8.5%. To investigate the hypothesis that 5-FU induces arterial vasospasm, 105 rings of rabbit aorta were mounted isometrically with 2 g resting tension in Kreb's buffer and exposed to 5-FU $7x10^{-9}$-$7x10^{-3}$M. Magnitude (mag) of vasoconstriction (CON) was expressed as % maximum CON in response to 5-FU $7x10^{-3}$M. CON was observed in 20/86 (23%) rings exposed to 5-FU $7x10^{-5}$ M (mag=10.8±3.1%, m±SEM); 45/83 (54%) rings exposed to 5-FU in therapeutic concentration $7x10^{-4}$ M (mag=32.2±4.8%, m±SEM) and 41/49 (84%) rings exposed to 5-FU $7x10^{-3}$ M (100%, absolute mag 239.7±35.4 mg, m±SEM). CON lasted 4-16 min and was independent of endothelium integrity. Pretreatment with phentolamine 10^{-5}M; propranolol 10^{-6}M; diltiazem 10^{-5}M; H1 inhibitor diphenhydramine 10^{-5} M; H2 inhibitor cimetidine 10^{-5}M; cyclooxygenase inhibitor indomethacin 10^{-5} M did not alter mag of CON. Related compounds and other anti-neoplastic agents including uracil, thioguanine, methotrexate, cyclophosphamide, doxorubicin and leucovorin did not cause in vitro vasoconstriction in this model. Conclusions: 1) 5-FU induces vascular smooth muscle CON in vitro, supporting vasospasm as explanation for cardiovascular and cerebrovascular ischemic events in patients receiving 5-FU; 2) pretreatment with cell membrane receptor blockers failed to prevent 5-FU induced CON implying direct intracellular effect of 5-FU.

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Author Present: 10:00AM–11:00AM
Hall F, West Concourse
Pharmacology: Experimental

INCREASED NEPHROGENOUS ENDOTHELIN GENERATION DURING RADIOCONTRAST ADMINISTRATION.

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Endothelin (ET) is a potent endogenous vasoconstrictor peptide with preferential renal hemodynamic effects. Recent studies suggest that ET may act as a renal autocoid and mediate decreases in glomerular filtration rate (GFR) in pathophysiologic states such as renal ischemia and cyclosporin nephrotoxicity. Radiocontrast-induced nephropathy (RCIN) is an important cause of acute renal failure in which a role for ET has not yet been identified. We therefore tested the hypothesis that renal generation of ET is increased in association with acute decreases in GFR in response to radiocontrast administration. Using a recently developed animal model of RCIN in dogs with experimental heart failure, we measured GFR, plasma ET and fractional excretion of ET (FE_{ET}), a marker for nephrogenous ET production, before and during administration of radiocontrast (iothalamate meglumine 52%, and iothalamate sodium 26%, 7 ml/kg iv over 10 min). These responses were assessed in the presence and absence of an intraaortic infusion of atrial natriuretic factor (ANF), 30 ng/kg/min, which we have recently demonstrated prevents RCIN in this model.

	CHF Only		CHF with ANF	
	Before RC	During RC	Before RC	During RC
GFR (ml/min)	26.7±5.0	17.2±3.9 *	32.1±3.9	27.4±4.3
ET (pg/ml)	16.9±3.8	19.2±5.2	23.8±4.6	28.8±8.2
FE_{ET} (%)	9.1±3.7	51.1±18.1*†	18.3±11.0	18.2±4.4

* $p<0.05$ vs Before RC, † $p<0.05$ vs CHF with ANF Group
'RC' denotes radiocontrast administration

These studies indicate that increases in nephrogenous production of ET, independent of changes in circulating ET, accompany acute radiocontrast-induced reductions in renal function in experimental CHF. Prevention of early changes in GFR and nephrogenous ET generation may account for the protective action of ANF in this model of RCIN.

LOW DENSITY LIPOPROTEIN INDUCES PLATELET-DERIVED GROWTH FACTOR EXPRESSION IN VASCULAR SMOOTH MUSCLE CELLS

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The aim of this study was to determine the effect of LDL on platelet-derived growth factor (PDGF) A chain transcription in vascular smooth muscle cells (SMC). Methods: Rat aortic SMC were cultured in DMEM + lipoprotein deficient serum for 48 hr and in DMEM + serum free medium for an additional 48 hr. Cells were then incubated with 250 ug/ml LDL (experimental group, LDL) or without LDL (negative control, C) for 6 hours. A human osteogenic sarcoma cell line served as positive control (U-2OS). Total RNA was extracted and assayed for the presence of PDGF A chain mRNA transcripts using a 1.3 kbp human PDGF A chain cDNA probe. Results: LDL increased the signal intensity of all three PDGF A transcripts, especially that of the 2.3 kb. Relative density of PDGF A transcripts on the Northern blot was:

	C	LDL	U-2OS
2.9kb	6,887	301,330	386,880
2.3kb	10,669	621,690	694,480
1.7kb	48,664	85,203	87,472

Conclusion: LDL is a strong and selective activator of PDGF A transcription in cultured vascular SMC. LDL may have a role in the initiation of SMC proliferation via induction of PDGF A expression.